REMARKS

By virtue of this amendment, claims 1-18 have been canceled without prejudice and new claims 19-26 have been added. No new subject matter has been added by these amendments. claims 19-26 are thus pending in the present application. Applicants submit that the present amendments place this application in condition for allowance for at least the reasons set forth below.

With regard to the addition of new claims 19-26, claim 19 recites a method of treating a diet-induced fatty liver disease by administering an α_1-adrenoreceptor antagonist, a β_2-adrenoreceptor agonist, or a combination thereof. "α_1-adrenoreceptor antagonist" is referenced throughout the present application. For example, reference may be made to page 1, paragraph 5 of the present application and Figure 6, which confirm the presence of α_1-adrenoreceptors in the hepatic progenitor cells of interest. Equally, "β_2-adrenoreceptor agonist" is referenced, for example, on page 12, paragraphs 114-116 and page 12, paragraphs 123 and 126 of the present application. These passages clearly indicate that the hepatic progenitor cells of interest express β_2-adrenoreceptors and that agonism of such receptors leads to the effect of hepatic accumulation of such progenitor cells.

"Diet-induced fatty liver disease" also finds clear support in the present application since it is evident from the description of the animal model employed that the liver disease being examined is diet-induced and, from the resulting pathophysiological characteristics, that the model is one of fatty liver disease (see page 7, paragraph 78 of the present application, indicating hepatic steatosis and necrosis). Indeed, one skilled in the art would appreciate that the experimental diet used to induce the liver injury in the animal model (methionine and choline deficient, with ethionine supplementation) is an antioxidant-depleted regimen which is known to

lead to fatty liver disease. Accordingly, it is submitted that the skilled artisan would find clear support for the term "diet-induced fatty liver disease" from the description of the present application.

New claim 20 is based on claim 5 as originally filed, read in conjunction with page 12, paragraphs 113 to 115 of the present application, which illustrates that the predominant sub type of α_1-adrenoreceptor on the hepatic progenitor cells of interest is the α_{1B}-adrenoreceptor.

New claim 21 is based on claim 9 as originally filed. Further, new claim 22 states that the β_2-adrenoreceptor agonist is isoprenaline. Basis for this can be found from the experiments described on pages 12 to 13 of the present application where isoprenaline is used as an exemplary β_2-adrenoreceptor agonist.

New claims 23-26 specify that the diet-induced fatty liver disease is non-alcoholic fatty liver disease. As noted above, one skilled in the art would immediately appreciate that the model of liver injury employed in the studies described in the present application is representative of fatty liver disease induced by diet. The skilled artisan would also know that such disease is commonly characterized as non-alcoholic fatty liver disease. In this regard, the Applicants also refer to the enclosed papers by Weltman et al. (1996) and Kirsch et al. (2003), which confirm that the skilled artisan would have immediately understood that the animal model described in the present application was suitably representative of non-alcoholic fatty liver disease (or non-alcoholic steatohepatitis, the more severe stage of non-alcoholic fatty liver disease).

Objections

In the Office Action of January 14, 2008, the Patent Office has objected to the disclosure of the present application due to several minor informalities. These informalities have been addressed by the present amendments. In particular, the misspelling of the word "prazosin" in the abstract has now been corrected by a replacement abstract, which is appended to this response. Further, the term "adrenoceptor" has been amended to "adrenoreceptor" throughout the claims, despite the terms being interchangeable and both being commonly used in the art.

35 U.S.C. §112, Second Paragraph Rejections

The Patent Office has rejected Claims 11-18 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Further, the Patent Office has also rejected Claims 11-18 under 35 U.S.C. §101, asserting that the recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process. In so far as applied to the claims, as amended, these rejections are respectfully traversed and should be withdrawn.

Claims 11-18 of the present application have now been canceled by virtue of the present amendments and new claims 19-26 have been added. As such, the claims of the present application are now directed towards a method of treating a diet induced fatty liver disease, which comprises the step of administering an α_1-adrenoreceptor antagonist, a β_2-adrenoreceptor agonist, or a combination thereof to a subject in need of treatment. As such, Applicants respectfully submit that the claims, as amended, comply with the provisions of 35 U.S.C. §112,

second paragraph and 35 U.S.C. §101, and Applicants respectfully traverse the rejection and request that it be withdrawn.

35 U.S.C. §112, First Paragraph Rejections

The Patent Office has rejected Claims 1-8, 10-16, and 18 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Patent Office has asserted that the species disclosed as agents for mobilizing stem cells are not representative of the genus because the genus is highly variant. Without addressing the merits of the Patent Office's rejection, this rejection has now been rendered moot by virtue of the cancellation of Claims 11-18, as well as the inclusion of Claims 19-26, which do not recite "an agent for mobilizing stem cells." Accordingly, applicants respectfully traverse the rejection.

Further, with regard to the presently-pending claims, the terms "α_1-adrenoreceptor antagonist" and "β_2-adrenoreceptor agonist" should be regarded as clear in their meaning and scope. It is thus submitted that the present application meets the written description requirement with respect to these terms. Additionally, it is submitted that at the earliest priority date of the present application, such terms would have been as familiar and understandable to the person skilled in the fields of physiology and pharmacology as terms such as "adhesive", "fixing means", "compressible" or "resilient" would have been to one skilled in the mechanical arts. One skilled in the art would immediately have been able to come up with a list of compounds which he would have known would have the properties of α_1 antagonism or β_2 agonism.

Furthermore, any compounds presented to the skilled person and which were not in his "immediate list" could be readily tested, using standard protocols available at the time, to determine whether they had the required characteristics.

It is submitted that such functional language should be allowed if the invention cannot otherwise be defined more precisely without unduly restricting the scope of the claims and if the functional result is one which can be directly and positively verified by tests known to the person skilled in the art and which do not require undue experimentation. It is also submitted that the terms used in the enclosed claims fit precisely within this framework of allowable functional claim language. α_1 antagonism or β_2 agonism could have been readily determined by the skilled person and, to require the compounds to be used according to the claims to be defined more precisely would undoubtedly result in an undue restriction of the scope thereof. Even if the current specification listed every α_1-adrenoreceptor antagonist and β_2-adrenoreceptor agonist known to exist at the filing date, restriction to such a list could still be regarded as an undue curtailment of scope since a third party could design further compounds having such properties and thereby take advantage of the fundamental concept of the claimed invention. As the Patent Office will appreciate, a restriction of claim 19 from the present language to specific compounds having basis in the application as filed could have a marked effect on the scope of the claims. It is respectfully submitted that such a restriction in scope is unwarranted.

Specifically in relation to the written description requirement, it is submitted that the present specification does indeed illustrate that the present inventors were in possession of the invention as now claimed at the time of filing. The terms "α_1-adrenoreceptor antagonist" and "β_2-adrenoreceptor agonist" are terms which would readily enable the skilled person, from his common general knowledge, to immediately recognize which agents were under consideration.

The present specification illustrates that a model compound from each of these classes is suitable and efficacious for carrying out the claimed invention. Notwithstanding the Patent Office's comments regarding the variability of the genus of agents potentially covered by the wording of the previous set of claims, it is believed that the enclosed amended claims now provide a restricted definition of pharmaceutical agents which would not suffer from such variability. Accordingly, it is submitted that the written description requirement has been met and applicants therefore respectfully request withdrawal of this rejection.

35 U.S.C. §102 Rejections

The Patent Office has also rejected Claims 1-3, 5, 6, 9, 11, 13, 14, and 17 under 35 U.S.C. §102(b) as being anticipated by McLean (U.S. Patent No. 6,174,917); and, has rejected Claims 1-3, 5, 6, 9, 11, 13, 14, and 17 under 35 U.S.C. §102(e) as being anticipated by Dubuisson et al. (U.S. Patent No. 6,649,615). In so far as applied to the claims as amended, these rejections are respectfully traversed for the reasons set forth below.

By virtue of the present amendments, claims 1-18 have been canceled and claim 19 added. Applicants respectfully submit none of the prior art documents cited by the Patent Office teaches or suggests, alone or in combination, each and every element of newly added claim 19. Specifically, McLean relates to the general use of vasodilating agents for the treatment of specific liver diseases by means of an alleged increase in hepatic arterial blood flow. Further, McLean discusses various agents in abstract terms, but actually only employs two agents in the tests reported therein, namely, diltiazem, (McLean, column 1, line 16), and nitroglycerine (McLean, column 8, first and second paragraphs). The former is a calcium channel blocker, the

latter a nitric oxide donor. Neither agent is an α_1 adrenoreceptor antagonist or a β_2 adrenoreceptor agonist. Notwithstanding the fact that the main thrust of this reference is to the use of a calcium channel blocker, rather than the compounds described and claimed for use in the methods of the present application, it is clear that the claims of the present application relate to the treatment of a condition not even mentioned, let alone described by McLean, namely, as set out above, diet-induced fatty liver disease or non-alcoholic fatty liver disease. McLean's model of disease (carbon tetrachloride induced liver disease), did not encompass the diseases now claimed.

In addition, no specific evidence is provided in McLean for the efficacy of prazosin or indeed the other groups of vasodilators that are referred to in this reference (other than diltiazem). In order for a reference to serve as a valid prior art reference, the reference must provide an enabling disclosure. MPEP §2121.01; *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 68 USPQ2d 1373 (Fed. Cir. 2003). Accordingly, McLean does not provide a sufficiently enabling disclosure of the use of α_1 adrenoreceptor antagonists or β_2 adrenoreceptor agonists in the treatment of diet-induced fatty liver disease. Rather, the disclosure is at best speculative in relation to such agents. Since McLean is not enabling with respect to the use of these agents, it does not constitute an enabling disclosure with respect to their use in the specific condition of diet-induced fatty liver disease, as presently claimed. Further, McLean does not teach or suggest at all the treatment of a diet-induced fatty liver disease.

It is also respectfully submitted that the other cited reference, Dubuisson (US 6,649,615), also fails to teach or suggest the use of an α_1-adrenoreceptor antagonist or a β_2-adrenoreceptor agonist for the treatment of diet-induced fatty liver disease. In particular, this reference relates

only to the effect of prazosin (or 6-hydroxydopamine, an adrenergic denervating agent) on liver fibrogenesis in animals, again like in McLean, treated with the toxin carbon tetrachloride. No teaching or even suggestion is made of treating diet-induced fatty liver disease. Only fibrosis inhibition is considered.

Diet-induced fatty liver disease, or non-alcoholic fatty liver disease, is distinct from other liver diseases, of which there are approximately ten major chronic types. Further, fibrosis is not even a liver disease *per se*. All tissue injuries, whether hepatic or otherwise, tend to result in fibrosis since this is the body's default wound healing response to injury. Treatment merely of the consequential fibrosis which is observed in diet-induced fatty liver disease is essentially palliative; it removes the scar tissue which has formed but does not address the underlying problem in diet-induced fatty liver disease. This underlying problem is the oxidant stress and the resultant inhibition of hepatocyte replication and any effective treatment of diet-induced fatty liver disease would therefore need to maintain the "functional integrity" (i.e. the biochemical capabilities) of the liver by providing for its regeneration.

There is no teaching or suggestion in McLean or Dubuisson that the effects of the agents used therein go beyond vasodilatation or, speculatively, a reduction in fibrogenesis through an effect on stellate cells. One skilled in the art would have known that merely alleviating the effects of fibrosis by vasodilatation and increasing liver perfusion, or even by reducing stellate cell activity, would be of no use in diet-induced fatty liver disease without a concomitant regeneration of functional integrity in the liver. There is no teaching or suggestion in the cited prior art references that prazosin would have such an effect and hence the skilled person would not know or have expected it to be of any use in the treatment of diet-induced fatty liver disease.

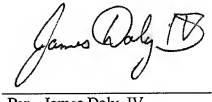
The cited prior art references merely present a model which relates the apparent effectiveness of the agents disclosed therein to their vasodilatory activity.

Accordingly, it is respectfully submitted that each and every element of the pending claims of the present application are not taught or suggested by the cited references. In particular, neither of the cited references, alone or in combination, teaches or suggests methods of treating a diet-induced fatty liver disease by administering to a subject in need of treatment for a diet-induced fatty liver disease treatment an α_1-adrenoreceptor antagonist, a β_2-adrenoreceptor agonist. Applicants therefore respectfully request withdrawal of these rejections.

In light of the amendments and arguments provided herewith, Applicants submit that the present application overcomes all prior rejections and objections, and has been placed in condition for allowance. Such action is respectfully requested.

Respectfully submitted,

Date: April 10, 2008



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